Oxidation of Primary Amines to Oxaziridines Using Molecular Oxygen (O_2) as the Ultimate Oxidant

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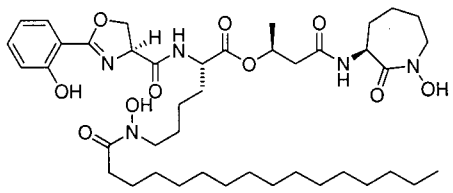
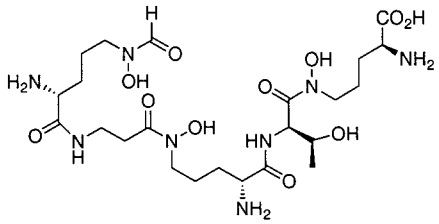
Introduction

Hydroxylamines are important synthetic precursors for hydroxamic acids that are found in many natural products, including microbial iron(III) chelators (siderophores).[1] Many unnatural hydroxamic acids also have significant biological activity, perhaps most notably as matrix metalloproteinase inhibitors.[2] The most straightforward synthesis of hydroxamates is the *N*-acylation of hydroxylamines. Due to the biological significance of hydroxylamines, development of methods for syntheses of *N*-alkyl hydroxylamines continues to attract attention.[3] Scheme 1 summarizes some of the currently available chemical synthetic methods for oxidation of primary amines to hydroxylamines. Most recently, a direct microwave-induced oxidation of primary amines **1** with oxone over silica gel or alumina was reported.[4] Another oxidation employed dimethyldioxirane (DMD) as the oxidant to afford nitrone **2**. Nitrone **2** can be hydrolyzed under acidic conditions or treated with hydroxylamine to afford the desired *N*-alkyl hydroxylamine **3**.[5] Formation of the nitrone intermediate avoids overoxidation. Similarly, prior alkylation of amines with α-haloacetonitrile followed by *m*-CPBA oxidation gives nitrone derivatives **4**, which can be converted into the desired *N*-alkyl hydroxylamines.[6] Alternatively, overoxidation can also be avoided through the indirect oxidation of primary amines **1**.[7] Primary amines can be first converted into aryl-derived imines **5**, which can be oxidized to afford 3-aryl oxaziridines **6**.[8] Acid-catalyzed isomerization of oxaziridines **6** affords stable α-aryl nitrones **7**.[9] Acid-catalyzed hydrolysis of either oxaziridines **6** or nitrones **7** gives hydroxylamines **3**. On the other hand, when the substituent in oxaziridine (**9**) is an alkyl group instead of an aryl group, N−O bond cleavage of the three-membered ring predominates to give the corresponding amide **10**.[10]



14, mycobactin S



15, exochelin MS

Figure 1. Structures of representative microbial iron chelators (siderophores) that contain hydroxamic acids that are essential for iron chelation.

Molecular oxygen (O_2) has been used as the ultimate oxidant in transition metal catalyzed Baeyer−Villiger oxidations of ketones to lactones and epoxidations of alkenes to epoxides.[11] This transition metal catalyzed oxidation features the in situ generation of peracid from aldehydes.[12] The advantage of this oxidation protocol is the utilization of oxygen as an inexpensive and safe source of oxidant, avoiding the use of large quantities of peracid, especially in industrial settings.

Despite this advantage, the use of molecular oxygen as the ultimate oxidant in oxidizing imines to oxaziridines received little attention until 1995.[13] Jorgensen and Martiny reported the first transition metal catalyzed oxidation of imines **11** to oxaziridines **12** by employing molecular oxygen as the oxidant in the presence of an aliphatic aldehyde as the co-reductant (Scheme 2). Under these catalytic oxidation conditions, imines that have a secondary or tertiary alkyl group at R_3 give oxaziridine **12** in high yield. However, when R_3 is a primary alkyl group, this catalytic oxidation affords the desired oxaziridine **12** only in low yield, but gives substantial amounts of byproducts such as alternate oxaziridine **13**.

Lysine-based and ornithine-based hydroxamates are important building blocks for mycobactins[14] (**14**) and exochelin MS[15] (**15**, Figure 1, respectively). The *N*-alkyl groups of these siderophores (microbial iron chelators) and many other hydroxamate-derived siderophores are often primary alkyl groups. In connection with our interests in the syntheses of siderophores, siderophore analogues, and siderophore−drug conjugates for biological studies,[16] we decided to expand the scope of the reported catalytic oxidation method to oxidize imines to

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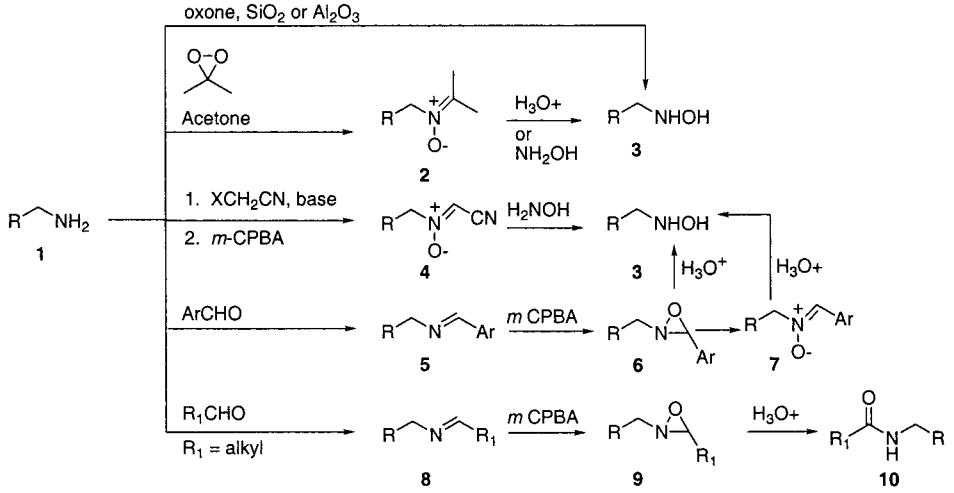
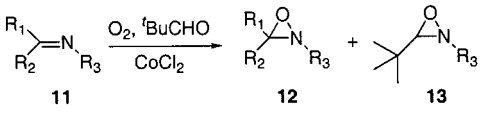
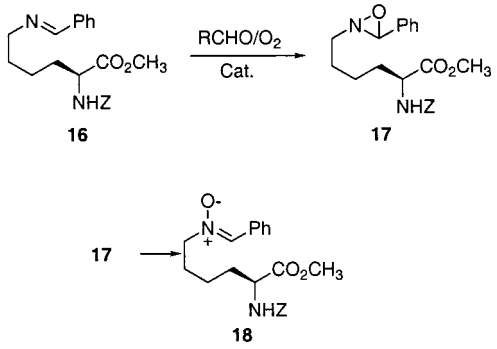
Scheme 1



Scheme 2



Scheme 3

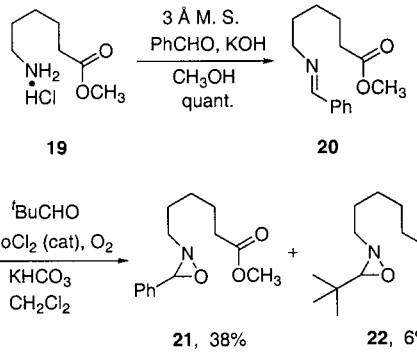


oxaziridines containing *primary* alkyl groups on nitrogen. Herein, we report detailed studies of a cobalt-catalyzed process with molecular oxygen that allows oxidation of imines from primary alkylamines, including imine **16** derived from L-lysine methyl ester (Scheme 3). Isomerization of the resulting 3-phenyloxaziridine **17** gives α-phenyl nitrone **18**, a stable protected form of key hydroxylamine siderophore components.[17]

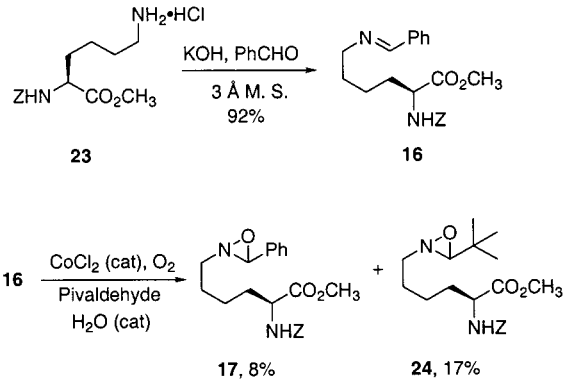
Results and Discussion

The Co(II)-mediated catalytic oxidation reaction was first examined using 6-aminocaproic acid methyl ester **19** as a model substrate. Treatment of methyl ester **19** with benzaldehyde in the presence of molecular sieves afforded the desired imine (**20**) in quantitative yield (Scheme 4). Under 1 atm of oxygen, imine **20** was oxidized to give about a 6:1 ratio of oxaziridines **21** and **22** in the presence of 5 mol % of cobalt chloride and 2 equiv of pivaldehyde. Indeed, this oxidation proved to be irreproducible in the amount of the undesired oxaziridine **22** produced.

Scheme 4



Scheme 5



When the above catalytic oxidation protocol was attempted on imine **16** derived from N^2-Cbz-L-lysine methyl ester (Scheme 5), however, no oxidation reaction occurred. Addition of a small quantity of water initiated the reaction immediately as indicated by rapid color changes in the reaction mixture. The desired oxaziridine **17** was isolated only in 8% yield, and the undesired oxaziridine **24** was isolated in 17% yield.

The formation of oxaziridines **22** and **24** in the above oxidation reactions was intriguing. We speculated that a rapid imine exchange reaction catalyzed by moisture present in the reaction mixture could occur to give a mixture of imine **26** and **28** under the reaction conditions (Scheme 6). Imine **28** formed during the reaction was also oxidized to give the undesired oxaziridine **29**. Under extremely dry reaction conditions, to suppress this imine exchange process, however, no catalytic oxidation of

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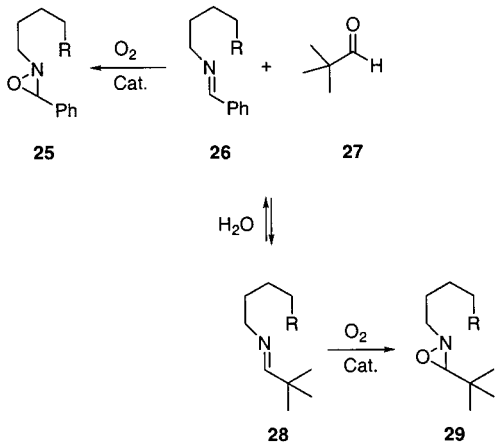
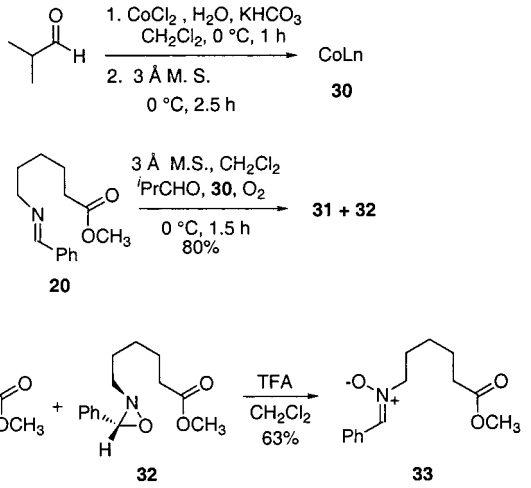
Scheme 6



Scheme 7

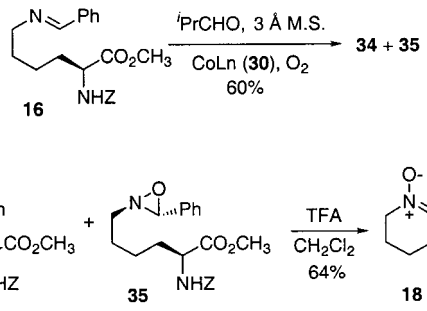


imine **26** was observed. Water apparently played a pivotal role in this catalytic oxidation of imines. Also, it was observed that successful catalytic oxidation reactions always gave rise to an olive green color. Finally, attempts to use benzaldehyde as the co-reductant were unsuccessful.

We then carried out a series of control experiments to determine the role water played in this cobalt-catalyzed reaction. Isobutyraldehyde was chosen as the co-reductant because it was cheaper than pivaldehyde. A vigorously stirred mixture of anhydrous cobalt(II) chloride, potassium bicarbonate, and isobutyraldehyde in methylene chloride gave no apparent color changes after 5 h at 0 °C or at room temperature. Addition of 0.1% (v/v of methylene chloride used) of water resulted in a color change in less than 15 min and gave the desired green color within 0.5 h. In the absence of potassium bicarbonate, the color change took a much longer time.

The addition of water apparently increased the solubility of $CoCl_2$ in methylene chloride. Isobutyraldehyde then coordinated to the solublized cobalt(II). The presence of $KHCO_3$ facilitated this ligand exchange reaction and presumably formed a cobalt aldehyde complex CoLn (**30**, Scheme 7), as indicated by color changes. This complex indeed catalyzed the O_2-mediated oxidation of imines to oxaziridines in the presence of isobutyraldehyde, although the undesired oxaziridine resulting from the imine exchange reaction was also observed. Addition of molecular sieves as a drying agent to the catalyst mixture

Scheme 8



eliminated the imine exchange problem. Indeed, when the green catalyst was dried by stirring with molecular sieves at 0 °C for 2.5 h before the substrate was added, catalytic oxidation of imine **20** employing the O_2/isobutyraldehyde system afforded the desired *cis*-oxaziridine **31** and *trans*-oxaziridine **32** in a combined 80% yield. Under these optimized reaction conditions, *none of the undesired oxaziridine was observed*. A mixture of oxaziridines **31** and **32** was isomerized to nitrone **33** in 63% yield when treated with TFA.

This improved catalytic oxidation procedure was successfully extended to the lysine-derived imine **16** (Scheme 8). In the presence of molecular sieves, subjecting imine **16** to the preformed catalyst **30** afforded the desired *cis*-oxaziridine **34** and *trans*-oxaziridine **35** in 60% combined yield. Again, undesired oxaziridine resulting from the imine exchange process was not observed. Isomerization of oxaziridines **34** and **35** with TFA gave the desired nitrone **18** in 64% yield. We have previously shown that nitrones such as **18** are readily converted to the corresponding hydroxylamines and hydroxamic acid components needed for syntheses and studies of important siderophores and analogues used for iron transport-mediated drug delivery.[9,14,16]

In summary, we have developed an improved procedure for the catalytic oxidation of imines to oxaziridines using cobalt as the catalyst and molecular oxygen as the ultimate oxidant. We have found that water plays an important role in the initial formation of the catalyst needed for this catalytic oxidation utilizing molecular oxygen. This modified protocol provides an alternative method for synthesizing *cis*- and *trans*-oxaziridines even from primary amines containing primary alkyl groups in high yield.

Experimental Section

General. All reactions were carried out under N_2 unless otherwise stated. Instruments and general methods used have been described previously.[9,14]

6-Aminocaproic Acid Methyl Ester (19). To 100 mL of methanol at 0 °C was added thionyl chloride (16.0 mL, 219 mmol). The solution was stirred at 0 °C for 20 min. To this solution at 0 °C was added 6-aminocaproic acid (13.0 g, 100 mmol). The solution was stirred at room temperature for 3.5 h. The volatiles were removed, and the residue was recrystallized from hexanes/ethyl acetate/methanol to give 17.9 g (quantitative) of methyl ester **19** as a white solid. Mp 120.0−121.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (br, 3H), 3.67 (s, 3H), 3.05 (br, 2H), 2.35 (t, J = 7.2 Hz, 2H), 1.84 (m, 2H), 1.65 (m, 2H), 1.46 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 51.2, 34.4, 33.3, 26.7, 25.6, 23.8. IR (KBr) 3444, 1731, 1617, 1577 cm^{-1}.

Imine 20. To a solution of KOH (1.12 g, 20.0 mmol) in methanol (50 mL) at room temperature were added methyl ester **19** (3.60 g, 20.0 mmol), benzaldehyde (2.12 mL, 20.9 mmol), and 3 Å molecular sieves. The mixture was stirred at room temper-

ature for 24 h. The molecular sieves were filtered off and washed with methanol. The filtrate was concentrated to give 5.03 g (quantitative) of imine **20** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.71 (m, 2H), 7.36 (m, 3H), 3.61 (s, 3H), 3.57 (t, J = 6.6 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.69 (m, 4H), 1.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 160.3, 135.9, 130.0, 128.1, 127.6, 60.9, 50.9, 33.5, 30.1, 26.4, 24.3. IR (neat) 1737, 1644, 1576, 1447, 1443, 1364 cm^{-1}.

Imine 16. To a solution of methyl ester hydrochloride **23** (1.25 g, 3.79 mmol) in methanol (20 mL) at room temperature were added KOH (0.223 g, 3.98 mmol) and benzaldehyde (0.40 mL, 3.94 mmol), followed by 3 Å molecular sieves. The reaction mixture was stirred at room temperature for 15 h. The solid was filtered off and washed with methanol. The filtrate was concentrated to give a residue, which was dissolved in methylene chloride (40 mL), and the insoluble material was filtered off. The methylene chloride filtrate was concentrated to give 1.39 g (92%) of imine **16** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.71 (m, 2H), 7.39 (m, 3H), 7.38 (m, 5H), 5.41 (d, J = 8.4 Hz, 1H), 5.08 (s, 2H), 4.38 (m, 1H), 3.69 (s, 3H), 3.58 (t, J = 6.6 Hz, 2H), 1.84−1.71 (m, 4H), 1.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 161.1, 155.8, 136.1, 130.5, 129.7, 129.0, 128.6, 128.5, 128.1, 128.0, 66.9, 61.1, 53.8, 52.3, 32.3, 30.3, 22.9. IR (neat) 3321, 1746, 1716, 1642 cm^{-1}. HRFABMS calcd for $C_{22}H_{27}N_2O_4$ (M + H$^+$) 383.1971, found 383.2000.

Catalyst 30. To a suspension of $CoCl_2$ (19.0 mg, 0.146 mmol) in methylene chloride (20.0 mL) at 0 °C were added $KHCO_3$ (35.0 mg, 0.35 mmol), isobutyraldehyde (0.33 mL, 3.64 mmol), and H_2O (20.0 μL). The mixture was stirred at 0 °C for 1 h. Then 3 Å molecular sieves were added and the mixture was stirred at 0 °C for another 2.5 h. The resulting green mixture was used as catalyst **30** in the following oxidation reaction.

Oxaziridines 31 and 32. To the above catalyst mixture at 0 °C was added a solution of imine **20** (0.70 g, 3.0 mmol) in methylene chloride (10 mL), followed by isobutyraldehyde (0.66 mL, 7.3 mmol). The mixture was degassed under vacuum and then stirred under an atmosphere of oxygen at 0 °C for 1.5 h. The solid was filtered through Celite and washed with methylene chloride. The filtrate was washed with half-saturated sodium bicarbonate, water, and brine, dried (Na_2SO_4), filtered, concentrated, and separated by flash column chromatography on Et_3N deactivated SiO_2 (8:1 to 4:1 hexanes/ethyl acetate) to give 0.60 g (80%) of oxaziridines **31** and **32**. For oxaziridine **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 5H), 5.26 (s, 1H), 3.64 (s, 3H), 2.45 (m, 2H), 2.25 (m, 2H), 1.66−1.52 (m, 4H), 1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 131.7, 129.4, 128.2, 127.8, 79.5, 52.8, 51.4, 33.8, 27.5, 26.7, 24.6; IR (neat) 1738, 1452, 1432 cm^{-1}; HRFABMS calcd for $C_{14}H_{20}NO_3$ (M + H$^+$) 250.1443, found 250.1448. For oxaziridine **32**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 4.49 (s, 1H), 3.66 (s, 3H), 3.22 (dt, J = 12.6, 7.2 Hz, 1H), 2.34 (dt, J = 12.3, 7.2 Hz, 1H), 2.34 (t, J = 7.5 Hz, 2H), 1.80−1.63 (m, 4H), 1.53−1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 134.7, 130.0, 128.4, 127.5, 80.4, 61.9, 51.4, 33.8, 27.6, 26.8, 24.7; IR (neat) 1732, 1457, 1437 cm^{-1}.

Nitrone 33. To a mixture of oxaziridines **31** and **32** (0.195 g, 0.783 mmol) at room temperature was added TFA (1 mL), followed by methylene chloride (1 mL). The resulting yellow solution was stirred at room temperature for 1 h, and the volatiles were removed to give an oily residue. To this residue were added 2:1 hexanes/ethyl acetate (10 mL), benzaldehyde (0.20 mL), and 3 Å molecular sieves. The mixture was stirred at room temperature for 18 h. The solid was filtered off, and the filtrate was concentrated and separated through flash column chromatography on SiO_2 (2:1 hexanes/ethyl acetate to ethyl acetate) to give 0.123 g (63%) of nitrone **33** as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (m, 2H), 7.42 (m, 3H), 7.39 (s, 1H), 3.94 (t, J = 7.0 Hz, 2H), 3.65 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 2.03 (m, 2H), 1.70 (m, 2H), 1.43 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 134.3, 130.4, 130.3, 128.5, 128.4, 66.9, 51.5, 33.7, 27.3, 25.9, 24.3. IR (neat) 1732, 1674, 1582, 1444, 1360 cm^{-1}. HRFABMS calcd for $C_{14}H_{20}NO_3$ (M + H$^+$) 250.1443, found 250.1452.

Oxaziridines 34 and 35. To a suspension of $CoCl_2$ (5.0 mg, 0.038 mmol) in methylene chloride (4 mL) at 0 °C were added $KHCO_3$ (9.0 mg, 0.090 mmol), isobutyraldehyde (0.085 mL, 0.937 mmol), and H_2O (4 μL). The mixture was stirred at 0 °C for 1 h. Then 3 Å molecular sieves were added and the mixture was stirred at 0 °C for another 2.5 h. The resulting green mixture was used as catalyst **30** in the following oxidation reaction. To the above catalyst at 0 °C was added a solution of imine **16** (0.300 g, 0.785 mmol) in methylene chloride (4 mL), followed by isobutyraldehyde (0.170 mL, 1.88 mmol). The mixture was degassed under vacuum and then stirred under an atmosphere of oxygen for 1.5 h. The solid was filtered through Celite and washed with methylene chloride. The filtrate was washed with half-saturated sodium bicarbonate, water, and brine, dried (Na_2SO_4), filtered, concentrated, and separated by flash column chromatography on Et_3N-deactivated SiO_2 (4:1 to 2:1 hexanes/ethyl acetate) to give 0.187 g (60%) of oxaziridines **34** and **35** as colorless oils. For oxaziridine **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 5H), 7.34 (m, 5H), 5.29 (d, J = 8.4 Hz, 1H), 5.25 (s, 1H), 5.09 (s, 2H), 4.32 (m, 1H), 3.72 (s, 3H), 2.42 (t, J = 6.9 Hz, 2H), 1.78−1.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 161.1, 155.8, 136.2, 131.6, 129.4, 128.5, 128.2, 128.1, 128.0, 127.8, 127.5, 79.4, 66.9, 53.7, 52.7, 52.6, 52.6, 32.3, 27.5, 27.4, 22.9; HRFABMS calcd for $C_{22}H_{27}N_2O_5$ (M + H$^+$) 399.1920, found 399.1922. For oxaziridine **35**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.30 (m, 10H), 5.35 (d, J = 8.1 Hz, 1H), 5.10 (m, 2H), 4.47 (s, 1H), 4.39 (m, 1H), 3.72 (s, 3H), 3.02 (m, 1H), 2.67 (m, 1H), 1.90−1.72 (m, 4H), 1.56−1.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 155.8, 136.2, 134.6, 130.0, 128.5, 128.4, 128.1, 128.0, 127.8, 127.5, 80.4, 66.9, 61.7, 61.6, 53.7, 52.3, 32.4, 27.5, 23.0, 22.9; IR (neat) 3341, 1746, 1724 cm^{-1}; HRFABMS calcd for $C_{22}H_{27}N_2O_5$ (M + H$^+$) 399.1920, found 399.1931.

Nitrone 18. To a mixture of oxaziridines **34** and **35** (0.316 g, 0.794 mmol) at room temperature was added TFA (2 mL), followed by methylene chloride (2 mL). The yellow solution was stirred at room temperature for 1 h, and the volatiles were removed. To the residue were added 2:1 hexanes/ethyl acetate (10 mL), benzaldehyde (0.2 mL), and 3 Å molecular sieves. The mixture was stirred at room temperature for 18 h. The molecular sieves were filtered off, and the filtrate was concentrated and separated by flash column chromatography on SiO_2 (2:1 hexanes/ethyl acetate to ethyl acetate) to give 0.202 g (64%) of nitrone **18** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24−8.20 (m, 3H), 7.40 (m, 3H), 7.34 (m, 5H), 5.47 (d, J = 8.1 Hz, 1H), 5.07 (s, 2H), 4.37 (m, 1H), 3.90 (t, J = 6.9 Hz, 2H), 3.69 (s, 3H), 2.04−1.76 (m, 4H), 1.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 155.9, 136.2, 134.4, 130.4, 128.5, 128.2, 128.1, 67.0, 66.7, 53.6, 52.4, 32.1, 27.1, 22.2. IR (neat) 3314, 3235, 1744, 1715, 1529, 1450 cm^{-1}. HRFABMS calcd for $C_{22}H_{27}N_2O_5$ (M + H$^+$) 399.1920, found 399.1915.

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Supporting Information Available: NMR spectra of compounds **18**, **19**, **20**, **22**, **31**, **32**, **33**, **34**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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